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09/537,654	03/29/2000	Pramod B. Mahajan	1107	7300

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EXAMINER
KUBELIK, ANNE R

ART UNIT	PAPER NUMBER
1638	8

DATE MAILED: 02/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/537,654	Applicant(s) MAHAJAN ET AL.	
	Examiner Anne R. Kubelik	Art Unit 1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-10,12 and 14-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-10,12 and 14-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 27 November 2002 has been entered.

2. The amendment to the title, the amendment of claims 2, 4, 8-9, 12 and 14-15, the cancellation of claim 13, and the addition of new claims 16-35 requested in Paper No. 17, filed 27 November 2002 have been entered. Claims 2-10, 12 and 14-35 are pending.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Amendment

4. The objection to the title of the invention as not being descriptive of the instant invention is withdrawn in light of amendment to the title.

5. The objection to claims 9 and 12-15 because of informalities is WITHDRAWN in light of amendments to the claims.

6. The rejection of claim 8 under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility is WITHDRAWN in light of amendments to the claims to state that the seed comprises the recombinant expression cassette.

7. The rejection of claim 14 is rejected under 35 U.S.C. 101 and under 35 U.S.C. 112, first paragraph because the claimed invention is not supported by either a specific asserted utility or a well-established utility is WITHDRAWN in light of amendments to the claims to state that the polynucleotide hybridizes to the full length complement of SEQ ID NO:1.

Claim Rejections - 35 USC § 112

8. Claims 2-10, 12, 14-16, 18-26 and 28-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acids of SEQ ID NO:1 or that encode SEQ ID NO:2, does not reasonably provide enablement for nucleic acids that have 90% identity to SEQ ID NO:1, that encode a protein that has 90% identity to SEQ ID NO:2, that hybridize to SEQ ID NO:1, that encode any 25 contiguous amino acids of SEQ ID NO:2, or that comprise any 50 contiguous nucleotides of SEQ ID NO:1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The rejection is repeated for the reasons of record as set forth in the Office actions mailed 8 November 2001 and 1 July 2002, as applied to claims 2-10 and 12-15. Applicant's arguments filed 27 November 2002 have been fully considered but they are not persuasive.

The claims are broadly drawn to a multitude of nucleic acids that have 90% identity to SEQ ID NO:1, that encode a protein that has 90% identity to SEQ ID NO:2, that hybridize to SEQ ID NO:1, that encode any 25 contiguous amino acids of SEQ ID NO:2, or that comprise any 50 contiguous nucleotides of SEQ ID NO:1, cells and plants transformed with those nucleic acids and a method of using those nucleic acids to modulate the level of maize RAD51 in a plant.

The instant specification, however, only provides guidance for construction of a cDNA library from B73 maize line (example 1) sequencing random clones from the cDNA library (example 2); BLAST analysis of the sequences (example 3) to identify those with homology to Arabidopsis RAD51C (example 4).

The instant specification fails to provide guidance for exact hybridization or amplification conditions and probes/primers to use in isolation of nucleic acids other than SEQ ID NO:.

The instant specification also fails to provide guidance for which amino acids of SEQ ID NO:2 can be altered and to which other amino acids, and which amino acids must not be changed, to maintain RAD51 activity of the encoded protein. The specification also fails to provide guidance for which amino acids can be deleted and which regions of the protein can tolerate insertions and still produce a functional enzyme.

One method of making alterations, making "conservative" substitutions (*e.g.*, substituting one polar amino acid for another, or one acidic one for another) does not produce predictable results. Lazar et al (1988, Mol. Cell. Biol. 8:1247-1252) showed that the "conservative" substitution of glutamic acid for aspartic acid at position 47 reduced biological function of transforming growth factor alpha while "nonconservative" substitutions with alanine or asparagine had no effect (abstract). Similarly, Hill et al (1998, Biochem. Biophys. Res. Comm. 244:573-577) teach that when three histidines that are maintained in ADP-glucose pyrophosphorylase across several species are substituted with the "nonconservative" amino acid glutamine, there is little effect on enzyme activity, while the substitution of one of those histidines with the "conservative" amino acid arginine drastically reduced enzyme activity (see

Table 1). All these mutated proteins, however, would have at least 95% identity to the original protein. The nucleic acids encoding all these mutated proteins, however, would hybridize under high stringency to the nucleic acids encoding the original protein.

Given the claim breath, unpredictability, and lack of guidance as discussed above, undue experimentation would have been required by one skilled in the art to develop and evaluate nucleic acids encoding proteins with 90% identity to SEQ ID NO:2. Making all possible single amino acid substitutions in an 294 amino acid long protein like that encoded by SEQ ID NO:1 would require making and analyzing 19^{294} nucleic acids; these proteins would have 99.6% identity to SEQ ID NO:2. Because nucleic acids encoding proteins with 90% identity to SEQ ID NO:2 would encode proteins with 29 amino acid substitutions, many more than 19^{294} nucleic acids would need to be made and analyzed.

As the specification does not describe the transformation of any plant with a gene encoding Rad51C, undue trial and error experimentation would be required to screen through the myriad of nucleic acids encompassed by the claims and plants transformed therewith, to identify those with modulated RAD51C, if such plants are even obtainable.

The nucleic acid of SEQ ID NO:1 is thought to encode a RAD51 protein, and RAD51 proteins are thought to have similar cellular functions to RecA (instant specification, pg 3, lines 3-16, and Thacker et al, 1999, Trends in Gen. 15:166-168). Plants transformed with a gene encoding the RecA protein unexpectedly do not have increased gene targeting, even though the plants had increased levels of intrachromosomal recombination (Reiss et al, 2000, Proc. Natl. Acad. Sci. 97:3358-3363, pg 3360-3362).

Given the claim breath, unpredictability, and lack of guidance as discussed above, undue experimentation would have been required by one skilled in the art to develop and evaluate nucleic acids that have 90% identity to SEQ ID NO:1, that encode a protein with 90% identity SEQ ID NO:2, that encode 25 contiguous amino acids of SEQ ID NO:2, or that comprise 50 nucleotides that hybridize to SEQ ID NO:1, cells and plants transformed with those nucleic acids and a method of using those nucleic acids to modulate the level of maize RAD51 in a plant.

Applicant urges that a patent need not teach what is well-known in the art, and a specification is not required to disclose all possible permutations as defined by the limitations of the claims. Applicant urges that the specification and the knowledge of one of skill in the art provide sufficient information and guidance to enable one of skill in the art to make and use the claimed nucleic acids. Applicant urges that the specification teaches three independent full-length Rad51C nucleic acid sequences and teaches one of skill in the art how to make the claimed nucleic acids. Applicant urges that it would not be necessary to make and assay every possible amino acid substitution, and that any experimentation necessary would be routine. Applicant urges that they have disclosed SEQ ID NO:1, 3 and 5, encoding RAD51 homologs, and provide guidance for analyzing, isolating, identifying and characterizing the sequences (response pg 9-12).

This is not found persuasive. The specification does not teach any nucleic acids that have 90% identity to SEQ ID NO:1, that encode a protein that has 90% identity to SEQ ID NO:2, that hybridize to SEQ ID NO:1, that encode any25 contiguous amino acids of SEQ ID NO:2, or that comprise any 50 contiguous nucleotides of SEQ ID NO:1. SEQ ID NOs:3 and 5 are 98.9% and 98.6% identical, respectively, to SEQ ID NO:1, and thus do not provide guidance for making

nucleic acids with 90% identity to SEQ ID NO:1, wherein the nucleic acids encoding proteins with the claimed function. Given the lack of guidance as to which amino acids to modify, undue trial and error experimentation would be required in making a nucleic acid encoding a protein with the 29 required amino acid substitutions to find one that makes a functional protein. Thus, the required experimentation would not be routine.

9. Claims 2-10, 12, 14-16, 18-26 and 28-35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is repeated for the reasons of record as set forth in the Office actions mailed 8 November 2001 and 1 July 2002, as applied to claims 2-10 and 12-15. Applicant's arguments filed 27 November 2002 have been fully considered but they are not persuasive.

Applicant urges that the claims are drawn to specific polynucleotides having a predictable structure represented by their sequence identity to SEQ ID NO:1. Applicant also urges that the claims following example 14 of the written description guidelines (response pg 12-13).

This is not found persuasive because Applicant has not described the structural features, *i.e.*, the sequence, of a nucleic acid that has 90% identity to SEQ ID NO:1 or that encodes a protein with 90% identity to SEQ ID NO:2. The specification also does not describe the 50 contiguous nucleotides or 25 contiguous amino acids encompassed by the claims, nor is any function for these nucleic acids recited. The specification does not describe nucleic acids that hybridize to SEQ ID NO:1 under the claimed conditions.

The claims also do not follow the format of Example 14 of the Written Description Guidelines. 90% identity is not the 95% identity used Example 14, and "participates in a complex which enhances recombinase activity" is not a specific description of function as used in the Guidelines.

10. Claims 2-10, 12, 14 and 16-34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Neither the instant specification nor the originally filed claims appear to provide support for the phrase "over the entire length of SEQ ID NO:1" in claim 12, part (a), "full-length complement of SEQ ID NO:1" in claim 14, lines 2-3 and "participates in a complex which enhances recombinase activity" in claim 12, part (a). Thus, such phrase constitutes NEW MATTER. In response to this rejection, Applicant is required to point to support for the phrase or to cancel the new matter.

Applicant's arguments filed 27 November 2002 in response to the previous new matter rejection have been fully considered but they are not persuasive. Applicant points to portions of the specification that define "reference sequence" and Gap penalty (response pg 13).

This is not found persuasive because Applicant did not point to evidence that supports the claimed nucleic acids hybridizing to or having identity to full-length portions of the sequences.

11. Claims 2-10, 12 and 14-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that

Applicant regards as the invention. Dependent claims are included in all rejections. The rejection is repeated for the reasons of record as set forth in the Office actions mailed 8 November 2001 and 1 July 2002, as applied to claims 2-10 and 12-14. Applicant's arguments filed 27 November 2002 have been fully considered but they are not persuasive.

Applicant urges that "selectively hybridizes" is defined in the specification and urges that the time of the wash is not an important factor, citing Ausubel et al (response pg 14).

This is not found persuasive because a wash of 30 minutes is much more stringent than a wash of 1 minute. Thus, the time of the wash is necessary to define the metes and bounds of the claimed nucleic acids. Ausubel et al could not be considered because it was not sent.

Claim 14 is indefinite in its recitation of the hybridization and wash conditions because the times are not recited.

The following rejections are new, as a result of amendments to the claims:

Claims 12, 14 and 25 are indefinite in their recitation of "polypeptide which participates in a complex which enhances recombinase activity". It is unclear what it means for a protein to participate in a complex. Would a protein that is involved in translation be considered to participate in such a complex – it would be required to make the proteins for the complex, and would interact with them at some point. It is also unclear what is means to enhance recombinase activity – enhance relative to what?

Claim Rejections - 35 USC § 102

12. Claim 14 is rejected under 35 U.S.C. 102(a) as being anticipated by NCI-CGAP (1998, GenBank Accession No. AI184177). The rejection is repeated for the reasons of record as set

forth in the Office actions mailed 8 November 2001 and 1 July 2002. Applicant's arguments filed 27 November 2002 have been fully considered but they are not persuasive.

Applicant urges that the specification defines "selectively hybridizing sequences" as those that "typically have at least 80% identity" (response pg 15).

This is not found persuasive because "typically" makes the definition simply an example, and other definitions are not excluded. The nucleic acid taught by NCI-CGAP would "selectively hybridize" to SEQ ID NO:1 under the claimed hybridization and wash conditions, given the lack of recitation of hybridization and wash times.

13. Claims 2-10, 12 and 15-35 are free of the prior art given the failure of the prior art to teach or suggest an isolated RAD51C encoding nucleic acid with 90% identity to SEQ ID NO:1, encoding a protein with 90% identity to SEQ ID NO:2, comprising 50 contiguous nucleotides of SEQ ID NO:1 or encoding 25 contiguous amino acids of SEQ ID NO:2. The prior art also fails to teach or suggest a recombinant expression cassette comprising a nucleic acid that hybridizes to SEQ ID NO:1.

Allowable Subject Matter

14. Claims 17 and 25 would be allowable if rewritten or amended to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action.

Conclusion

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (703) 308-5059. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at (703) 306-3218. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Customer Service at (703) 308-0196.

Anne R. Kubelik, Ph.D.
January 30, 2003

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